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8(e)

5578

# CAP

(COMPLIANCE AUDIT PROGRAM)

**TSCA CONFIDENTIAL BUSINESS INFORMATION**

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8EHQ-0792-5578 Init

July 9, 1992


88920004224

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**RETURN RECEIPT REQUESTED**

Document Processing Center (TS-790)
Office of Toxic Substances
U.S. Environmental Protection Agency
401 M St., S.W.
Washington, D.C. 20460

Attn: Section 8(e) Coordinator (CAP Agreement)

RE: Report Submitted Pursuant to the TSCA Section 8(e) Compliance Audit Program

CAP Identification Number: 8ECAP-0026

Dear Sir/Madam:

Pursuant to the Toxic Substances Control Act (TSCA) Section 8(e) Compliance Audit Program and the Agreement for TSCA Section 8(e) Compliance Audit Program (CAP Agreement) executed by Elf Atochem North America Inc. (Atochem) and Environmental Protection Agency (EPA), Atochem is submitting the enclosed final report on studies to establish skin and eye irritation potential in rabbits for tributyltin chloride to the EPA. These studies do not involve effects in humans.

Nothing in this letter or the enclosed studies is considered confidential business information of Atochem.

The enclosed studies provide information on the chemical tributyltin chloride. Its exact chemical name is tributylchlorostannane and its CAS number is 1461-22-9.

The title of the enclosed study report is Acute Toxicity Studies in Rats and Rabbits. This report consists of several studies. The following is a summary of the adverse effects observed in primary skin irritation and eye irritation studies in rabbits.

Application of 0.1 ml tributyltin chloride to the right eye of each of six albino rabbits was corrosive to the rabbit eye. Lavage with water after a 5 minute application of the test material to the right eye of each of an additional six rabbits did not reverse the corrosive effects. Application of 0.5 ml tributyltin chloride to the intact and abraded skin of groups of six albino rabbits for 24 hours and for 5 minutes was corrosive to rabbit skin.

To our knowledge, Atochem has not previously submitted any TSCA Section 8(e) notices or premanufacture notifications on the subject chemical.

Further questions regarding this submission may be directed to me at 215 337-6892.

Sincerely,

Craig

C.H. Farr, PhD, DABT
Manager, Product Safety
and Toxicology

Enclosures

FILED: CN444-85

TR91-325

CONTAINS NO CBI

*International Research and Development Corporation*

T-181

SPONSOR: M & T Chemicals, Inc.

COMPOUND: Tributyltin Chloride

SUBJECT: Acute Toxicity Studies in Rats and Rabbits.

Francis X. Wazeter, Ph.D.
Director of Research
International Research and
Development Corporation

Collaborators:

R. H. Buller, Ph.D.
R. G. Geil, D.V.M.
J. A. Rehkemper, D.V.M.

Date: December 15, 1967

221-024

CAS# 25245-64-1

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I. MATERIAL

The test compound was received from M & T Chemicals, Inc., Rahway, New Jersey on September 12th, 1967.

The test material was identified as "Tributyltin Chloride, C7RAR-3K." It was received as a clear liquid.

## II. SYNOPSIS

Tributyltin Chloride was examined for acute oral toxicity in rats and for dermal toxicity and skin and eye irritation in rabbits in accordance with the regulations of the Federal Hazardous Substances Labeling Act. In addition, certain additional modified tests were performed in order to more completely determine the toxicity and potential hazard to man of this agent . The results obtained in the various tests applied appear below:

1. Acute Oral Toxicity ($LD_{50}$) in Male Albino Rats:
   Greater than 50 mg./kg. but less than 500 mg./kg.; therefore a toxic substance.
2. Acute Dermal Toxicity ($LD_{50}$) in Albino Rabbits:
   Greater than 2000 mg./kg.; a non-toxic substance.
3. Eye Irritation in the Albino Rabbit (Standard Unwashed Technique):
   An eye irritant.
4. Eye Irritation in the Albino Rabbit (M & T Washed Eye Technique):
   An eye irritant.
5. Primary Skin Irritation in the Albino Rabbit (Standard Technique):
   A corrosive substance and probable primary skin irritant.
6. Primary Skin Irritation in the Albino Rabbit (M & T Technique):
   A corrosive substance and probable primary skin irritant.

III. ACUTE ORAL TOXICITY ($LD_{50}$) IN MALE ALBINO RATS

A. METHOD:

Charles River male albino rats weighing from 150 to 160 grams were used. The compound was orally administered at the following dosage levels: 50, 500 and 5000 mg./kg. Four rats were used at each dosage level.

All of the animals were fasted overnight prior to administration of the compound. The rats were group housed according to dosage level in cages suspended above the droppings. Food and water were available ad libitum.

The rats were observed for pharmacodynamic signs and mortality continously for five hours on the day of initiation and daily thereafter for a total of 14 days. All animals were subjected to necropsy examination.

The compound was administered as a suspension in corn oil at a volume of 1 ml./100 grams of body weight.

B. RESULTS:

1. Pharmacodynamic Signs and Mortality:

a. 50 mg./kg.:

All of the animals remained essentially normal throughout the 14 day period of observation. All of the rats at this dosage level survived the study period.

b. 500 mg./kg.:

Within 90 minutes following compound administration salivation, diarrhea and miosis were observed. From 90 to 300 minutes cyanosis, hypothermia, ataxia, and hypoactivity were observed.

At 24 hours two rats were found dead and the two surviving animals exhibited hypothermia, cyanosis, ataxia. One of the two surviving animals was prostate.

At 48 hours one of two surviving succumbed. The remaining animal showed salivation, diarrhea and hypothermia through the fourth study day.

At five days this animal was considered normal and survived the study period.

c. 5000 mg./kg.:

Within 30 minutes following oral intubation, dyspnea, salivation, diarrhea, hypothermia, miosis, cyanosis, hypoactivity and flaccidity were observed. These signs continued in evidence throughout the initial day of study.

At 24 hours all of the animals at this dosage level were found dead.

2. Necropsy Findings:

No gross lesions were found at necropsy in any rats which died as a result of compound administration or which were sacrificed at the end of the observation period.

3. Body Weight Gain:

All surviving animals exhibited normal body weight gains during the 14-day observation period.

4. Acute Oral Toxicity Evaluation in the Male Albino Rat:

Based upon the results obtained the acute oral toxicity in the male albino rat for Tributyltin Chloride would be greater than 50 but less than 500 mg./kg.

In accordance with the requirements of the Federal Hazardous Substances Labeling Act, Tributyltin Chloride, when administered in the manner described would be classified as a "toxic" substance.

IV. ACUTE DERMAL TOXICITY ($LD_{50}$) IN THE ALBINO RABBIT

A. METHOD:

Eight albino rabbits equally divided as to sex and weighing from 2350 to 2900 grams were used. The animals were divided into two groups of four rabbits each. The dorsal skin of each rabbit was prepared for treatment by close clipping of the hair with an electric clipper. In addition, the skin of one-half of the rabbits in each group was abraded by producing shallow incisions (not sufficiently deep to cause bleeding) with a scalpel blade over an area approximately three inches square. The proper amount of the test compound in mg./kg. was applied to the saline wetted back of each animal. The compound was then covered with surgical gauze which was held in place by wrapping the body with elastic bandage. This wrapping retarded evaporation and prevented oral ingestion. The compound was applied once only at dosage levels of 200 and 2000 mg./kg. of body weight .

All of the animals were immobilized for 24 hours in stocks during the application of the test material. At the end of the 24 hour period of restraint, the back of each animal was washed with tepid tap water and observed for evidence of dermal irritation. Thereafter, they were housed individually in metal cages suspended above the droppings with food and water available ad libitum.

The animals were observed daily for 14 days for evidence of pharmacotoxic signs and dermal irritation.

Individual body weights were obtained initially and at the termination of the study.

The skin reactions were scored according to the scale on the following page.

CODE

Erythema:

0 - None
1 - Very slight to slight
2 - Well defined or moderate
3 - Severe or marked

Eschar not graded only recorded same as necrosis, blanching, and hemorrhagic areas.

Edema:

0 - None
1 - Very slight to slight
2 - Moderate (raised 1.0 to 10 mm.)
3 - Marked (raised >10.0 mm.)

Atonia:

1 - Slight (sl. impairment of elasticity)
2 - Moderate (slow return to normal)
3 - Marked (no elasticity)

Desquamation:

1 - Slight (slight scaling)
2 - Moderate (scales and flakes)
3 - Marked (pronounced flaking with denuded areas)

Leathery Texture:

1 - Slight (decrease in pliability)
2 - Moderate (leathery texture)
3 - Marked (tough and brittle)

Fissuring:

1 - Slight (definite cracks in epidermis)
2 - Moderate (cracks in dermis)
3 - Marked (cracks with bleeding)

B. RESULTS:

1. Pharmacodynamic Signs and Mortality:

No adverse pharmacodynamic signs were observed at either dosage level tested during the 14-day observation period. One animal at the 2000 mg./kg. dosage level died in the 3rd day of study.

2. Necropsy Findings:

All rabbits which were sacrificed after the observation period had evidence of compound related dermal irritation as reported clinically. (see below). Most rabbits were in a poor state of nutrition. Rabbit 8373 (male, 2000 mg./kg.) also had slight pneumonia.

Rabbit 8374 (male, 2000 mg./kg.) which died on the third day of study had congestion of the right lung and marked congestion of the vasculative of the thoracic and abdominal muscles.

3. Dermal Irritation:

a. 200 mg./kg.:

All animals exhibited slight to moderate erythema and edema throughout the study period. Slight atonia was also noted throughout the 14 day study period. Desquamation (slight to marked) was observed in all of the animals tested and was first evidenced between the 7th and 11th study days.

Leathery texture (slight to moderate) was observed in two of four animals and fissuring (slight to moderate) in three of four rabbits. These signs were initially observed the 8th or 9th days of the observation period.

b. 2000 mg./kg.:

Erythema and edema (slight to moderate), were observed in all animals at this dosage level throughout the period of study.

Slight atonia was also observed daily in all animals.

Desquamation (slight to marked) was noted in two of four rabbits, being first evidenced from the 9th to the 11th day.

Leathery texture (slight) was observed in two of four rabbits and fissuring in one of four animals, both signs occurring from the 9th to the 14th study days.

All animals at both the 200 and 2000 mg./kg. dosage levels appeared sensitive to touch at the site of application during the observation period. Movement of these animals was generally inhibited apparently due to the dermal irritation noted. Necrosis and intra-dermal purulent exudate were observed in all animals at each dosage level. The irritation observed became progressively more marked with successive observation days following dermal application.

Table 1 presents the Daily Irritation Index for each of the above dosage levels. It can be noted in this table that the degree of irritation observed increased with successive days following dermal application of the test material.

4. Body Weight Gain:

All animals which survived the study period failed to show significant body weight changes which could be related to compound application with one exception. One female animal (#8371) at the 2000 mg./kg. dosage level exhibited a 500 gram loss in body weight during the first week of the observation period. This animal failed to regain any portion of this weight loss during the second week of the observation period.

5. Acute Dermal Toxicity Evaluation in the Albino Rabbit:

As only one mortality occurred in this study (2000 mg./kg. dosage level), the acute dermal toxicity of Tributyltin Chloride in the albino rabbit would be greater than 2000 mg./kg.

In accordance with the requirements of the Federal Hazardous Substances Labeling Act, Tributyltin Chloride when administered in the manner described would be considered as a non-toxic substance, however, this material does possess dermal irritant properties and should not be permitted contact with the human skin.

ibutyltin Chloride: Acute Dermal Toxicity ($LD_{50}$) in the Albino Rabbit.

BLE 1. Daily Dermal Irritation Index.

| imal No. / Group | Sex | Skin Preparation | Observation Days 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 0 mg./kg.: | | | | | | | | | | | | | | | | |
| 69 | M | Abraded | 0.25 | 0.41 | 0.51 | 0.58 | 0.66 | 0.83 | 1.08 | 1.00 | 1.33 | 1.91 | 1.91 | 1.93 | 1.83 | 2.08 |
| 70 | M | Intact | 0.41 | 0.58 | 0.75 | 0.66 | 0.83 | 1.00 | 1.08 | 1.16 | 1.58 | 1.91 | 2.08 | 2.06 | 2.16 | 2.08 |
| 67 | F | Abraded | 0.25 | 0.50 | 0.58 | 0.83 | 0.91 | 0.83 | 1.16 | 1.33 | 1.33 | 1.25 | 1.25 | 1.25 | 1.25 | 1.25 |
| 68 | F | Intact | 0.33 | 0.33 | 0.58 | 0.50 | 0.75 | 0.83 | 0.91 | 0.75 | 0.66 | 0.50 | 1.08 | 1.10 | 1.33 | 1.50 |
| mbined[1] | | | 0.31 | 0.46 | 0.61 | 0.64 | 0.79 | 0.87 | 1.06 | 1.06 | 1.23 | 1.39 | 1.58 | 1.59 | 1.64 | 1.73 |
| 00 mg./kg.: | | | | | | | | | | | | | | | | |
| 73 | M | Abraded | 0.53 | 0.41 | 0.33 | 0.58 | 0.50 | 0.50 | 0.58 | 0.58 | 0.83 | 0.91 | 0.75 | 1.02 | 1.25 | 1.16 |
| 74 | M | Intact | 0.25 | 0.25 | Died | | | | | | | | | | | |
| 71 | F | Abraded | 0.33 | 0.33 | 0.33 | 0.41 | 0.50 | 0.50 | 0.66 | 0.66 | 0.75 | 1.16 | 1.33 | 1.33 | 1.33 | 1.33 |
| 72 | F | Intact | 0.25 | 0.25 | 0.33 | 0.41 | 0.58 | 0.66 | 0.66 | 0.50 | 0.50 | 0.50 | 0.66 | 0.66 | 0.66 | 0.66 |
| mbined[1] | | | 0.34 | 0.31 | 0.33 | 0.47 | 0.53 | 0.55 | 0.63 | 0.58 | 0.69 | 0.86 | 0.91 | 1.00 | 1.08 | 1.05 |

quals the average of the combined scores for the animals employed in this dosage level group.

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V. EYE IRRITATION IN THE ALBINO RABBIT (Standard Technique)

A. METHOD:

Six albino rabbits, equally divided as to sex and weighing from 2040 to 2645 grams, were used. Throughout the study the rabbits were individually housed in metal cages suspended above the droppings. Food and water were available ad libitum.

One-tenth milliliter of the test material was instilled into the conjunctival sac of the right eye of each rabbit. The left eye served as the untreated control. None of the eyes were washed.

Prior to instillation of the test material, and again at the termination of the 72 hour observation period, both eyes of each animal were examined with the use of 2.0 per cent sodium fluorescein and a small-window, ultraviolet, quartz, mercury pencil lamp. Other observations for eye irritation were made on the day of application of the test material and again daily for three days thereafter. Eye irritation was graded and recorded according to the Method of Draize as described in the Manual "Appraisal of the Safety of Chemicals in Foods, Drugs, and Cosmetics", published by the Association of Food and Drug Officials of the United States, Business Office, Bureau of Foods and Drugs, Texas State Department of Health, Austin 1, Texas, 1959, pp. 49-51.

The cornea was scored on the basis of the density of opacity and the total area involved. The iris was scored on the intensity or degree of inflammation exhibited, and the palpebral and remaining bulbar mucosae were scored on the extent of chemosis, redness and discharge.

Under the standards of this test a substance was considered to be an irritant to the eye mucosa if there was, at any of the readings, and among any of the animals, discernible opacity of the cornea (other than a slight dulling of the normal luster) or ulceration of the cornea, or inflammation of the iris (other than a slight deepening of the folds (rugae) or a slight circumcorneal injection) or if such substance produced in the conjunctivae (excluding the cornea and iris) an obvious swelling with partial eversion of the lids or a diffuse deep-crimson red with individual vessels not easily discernible.

The scale for scoring ocular lesions appears on page 15.

B. RESULTS:

Each of the rabbits tested exhibited moderate to marked corneal opacity covering the entire corneal surface. This opacity was observed at 24 hours and continued in evidence at 48 and 72 hours.

Slight iridal irritation was also observed in all six rabbits at each period of observation.

Erythema (slight to marked), chemosis (marked) and discharge (slight to moderate) of the conjunctivae was observed in each rabbit at each observation interval.

All of the rabbits tested exhibited purulent discharge from the treated eye, necrosis of the conjunctival tissue and apparent blood in the anterior chamber during the observation period.

Table 2 page 16, presents the group average eye irritation scores obtained in this study.

Nasal discharge accompanied by respiratory congestion and dyspnea were also observed in each animal and were attributed to the instillation of the test material.

The eyes of all the animals were negative to sodium fluorescein examination prior to the instillation of the test material. Seventy-two hours following application, examination with sodium fluorescein revealed corneal opacity present in all rabbits.

According to the standards of this test, Tributyltin Chloride would be considered as a severe eye irritant when tested in the manner described.

## Scale for Scoring Ocular Lesions*

(1) Cornea

(A) Opacity-degree of density (area most dense taken for reading)

| | |
|---|---|
| No Opacity | 0 |
| Scattered or diffuse area, details of iris clearly visible | 1 |
| Easily discernible translucent areas, details of iris slightly obscured | 2 |
| Opalescent areas, no details of iris visible, size of pupil barely discernible | 3 |
| Opaque, iris invisible | 4 |

(B) Area of cornea involved

| | |
|---|---|
| One quarter (or less) but not zero | 1 |
| Greater than one quarter, but less than half | 2 |
| Greater than half, but less than three quarters | 3 |
| Greater than three quarters, up to whole area | 4 |

Score equals A x B x 5 Total maximum = 80

(2) Iris

(A) Values

| | |
|---|---|
| Normal | 0 |
| Folds above normal, congestion, swelling, circumcorneal injection (any or all of these or combination of any thereof) iris still reacting to light (sluggish reaction is positive) | 1 |
| No reaction to light, hemorrhage, gross destruction (any or all of these) | 2 |

Score equals A x 5 Total maximum = 10

(3) Conjunctivae

(A) Redness (refers to palpebral and bulbar conjunctivae excluding cornea and iris)

| | |
|---|---|
| Vessels normal | 0 |
| Vessels definitely injected above normal | 1 |
| More diffuse, deeper crimson red, individual vessels not easily discernible | 2 |
| Diffuse beefy red | 3 |

(B) Chemosis

| | |
|---|---|
| No swelling | 0 |
| Any swelling above normal (includes nictitating membrane) | 1 |
| Obvious swelling with partial eversion of lids | 2 |
| Swelling with lids about half closed | 3 |
| Swelling with lids about half closed to completely closed | 4 |

(C) Discharge

| | |
|---|---|
| No discharge | 0 |
| Any amount different from normal (does not include small amounts observed in inner canthus of normal animals) | 1 |
| Discharge with moistening of the lids and hairs just adjacent to lids | 2 |
| Discharge with moistening of the lids and hairs, and considerable area around the eye | 3 |

Score equals (A + B + C) x 2 Total maximum = 20

The maximum total score is the sum of all scores obtained for the cornea, iris, and conjunctivae. Total maximum score possible = 110.

* Lehman, A. J. et al., Appraisal of the Safety of Chemicals in Foods, Drugs, and Cosmetics, Assoc. Food and Drug Officials of the U. S., Austin, Texas, 1959.

Tributyltin Chloride: Eye Irritation Test in the Albino Rabbit. (Standard Technique).

TABLE 2. Group Average Values.

| Ocular Area | | Observation Periods Hours 24 | 48 | 72 |
|---|---|---|---|---|
| Cornea | A | 3.2 | 3.0 | 3.3 |
| | B | 4.0 | 4.0 | 4.0 |
| Cornea Score | | 64.0 | 60.0 | 66.0 |
| Iris | A | 1.5 | 1.3 | 1.6 |
| Iris Score | | 7.5 | 6.5 | 8.0 |
| Conjunctivae | A | 1.3 | 1.1 | 2.8 |
| | B | 4.0 | 4.0 | 4.0 |
| | C | 1.9 | 1.1 | 0.6 |
| Conjunctivae Score | | 14.4 | 12.4 | 14.8 |
| Total Score | | 85.9 | 78.9 | 88.8 |

VI. EYE IRRITATION IN THE ALBINO RABBIT (M & T Washed Eye Technique)

A. METHOD:

Six albino rabbits, undifferentiated as to sex and weighing from 1820 to 2430 grams, were used.

One-tenth mililiter of the test material was instilled into the conjunctival sac of the right eye of each rabbit. Exactly five minutes following the instillation of the test material, each treated eye was washed with five consecutive 20 ml. rinses of tepid tap water.

Other than as noted above, all other aspects of the method employed were as described for the standard technique in paragraph 5A.

B. RESULTS:

Five of six rabbits tested exhibited slight corneal opacity five minutes following instillation of the test material. Slight to moderate opacity was observed in all of the animals at 24, 48 and 72 hours.

The iris of the treated eye of three of six rabbits exhibited slight congestion five minutes following compound instillation. All animals exhibited slight iridal irritation at 24, 48 and 72 hours.

Irritation of the conjunctival tissue was observed in all of the animals tested and included erythema (moderate), chemosis (slight to marked), and discharge (slight).

Table 3 presents the group average eye irritation scores obtained in this study (see page 19).

Purulent exudate was observed from the treated eye of each of the animals. Necrosis of the conjunctional tissue was noted in five of six rabbits.

Nasal discharge, respiratory congestion and dyspnea were also observed and were attributed as being effects of the test material.

Both eyes of each rabbit were subjected to a sodium fluorescein examination prior to instillation of the test material and were found to be normal. Seventy-two hours after application each eye was similarly examined. The treated eye of each rabbit at this time showed complete opacity of the corneal surface.

The wash employed five minutes following instillation of the test material on the corneal surface did not significantly reduce the degree of irritation observed in the unwashed eye. (See paragraph V, B. of this report). The results of this test indicate that Tributyltin Chloride is an eye irritant and that washing of the corneal surface five minutes following instillation does not inhibit the adverse effects of this substance on the eye. Precaution should be exercised to prevent contact with the human eye.

Tributyltin Chloride: Eye Irritation Test in the Albino Rabbit (M & T Washed Eye Technique).

TABLE 3. Group Average Values.

| Ocular Area | | Observation Period Mins. 5 | Hours 24 | 48 | 72 |
|---|---|---|---|---|---|
| Cornea | A | 0.6 | 3.0 | 2.8 | 2.1 |
| | B | 2.3 | 4.0 | 4.0 | 4.0 |
| Cornea Score | | 6.9 | 60.0 | 56.0 | 42.0 |
| Iris | | 0.3 | 1.3 | 1.3 | 1.3 |
| Iris Score | | 1.5 | 6.5 | 6.5 | 6.5 |
| Conjunctivae | A | 1.0 | 1.5 | 2.3 | 3.0 |
| | B | 2.8 | 4.0 | 4.0 | 4.0 |
| | C | 0.0 | 1.3 | 0.8q | 0.8 |
| Conjunctivae Score | | 7.6 | 13.6 | 14.2 | 15.6 |
| Total Score | | 16.0 | 80.1 | 76.7 | 64.1 |

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VII. PRIMARY SKIN IRRITATION IN ALBINO RABBITS (Standard Technique)

A. METHOD:

A total of six albino rabbits, equally divided as to sex and ranging in weight from 1875 to 2390 grams were used. The animals were prepared for treatment by close clipping of the hair of the dorsal skin of each rabbit with an electric clipper. In addition, the clipped skin of one-half of the rabbits was abraded by producing shallow incisions with a scalpel blade over an area approximately three inches square.

The test compound was applied once only in a total amount of 0.5 ml. to the prepared back of each rabbit. Following application of the test material, the area of application was covered with gauze and each animal wrapped with an elastic bandage.

The animals were then immobilized in stocks for a period of 24 hours to permit percutaneous absorption and to prevent oral ingestion of the test material. At the end of the 24 hour period of confinement in the stocks, the bandages were removed and the back of each animal examined for evidence of irritation. The rabbits were then placed in individual metal cages suspended above the droppings with food and water available ad libitum. At the end of 48 and 72 hours, the backs were again examined for evidence of irritation.

All skin reactions were scored according to the code on the following page.

All skin reactions were scored according to the following scale:

| Erythema and Eschar Formation: | Value* |
|---|---|
| No erythema | 0 |
| Very slight erythema (barely perceptible) | 1 |
| Well defined erythema | 2 |
| Moderate to severe erythema | 3 |
| Severe erythema (beet redness) to slight eschar formation (injuries in depth) | 4 |

| Edema Formation: | |
|---|---|
| No edema | 0 |
| Very slight edema (barely perceptible) | 1 |
| Slight edema (edges of area well defined by definite raising) | 2 |
| Moderate edema (raised approximately 1.0 mm.) | 3 |
| Severe edema (raised more than 1.0 mm. extending beyond the area of exposure) | 4 |

* The "Value" recorded for each reading is the average value of 6 or more animals subjected to the test.

The values for erythema and eschar formation at 24 hours and at 72 hours for the intact animals' skin were added to similar values obtained for the abraded skin animals. (A total of 4 values).

Similarly, the values for edema formation at 24 and 72 hours for intact and abraded skin animals were added together (a total of 4 values). The primary irritant score is the sum of the 8 values divided by 4. As scored by this method, a primary irritant is a substance which is not corrosive, but which results in a score of 5 or more. (Section 191.1 (g) (2) of the regulations of the Federal Hazardous Substances Labeling Act).

B. RESULTS:

Tributyltin Chloride when applied to the back of the albino rabbit in the manner described produced slight to moderate erythema in four of six rabbits (two intact and two abraded). Erythema in the remaining two rabbits was precluded by necrosis. The degree of irritation observed was slightly increased at 48 and 72 hours when compared to that irritation observed at 24 hours. Edema (slight to marked) was observed in each of the six rabbits at 24, 48 and 72 hours. No significant difference was observed between abraded and intact skin animals.

In addition, necrosis and atonia were observed in all rabbits tested. Two of six animals also exhibited dyspnea following instillation of the test material.

Tributyltin Chloride, based upon the results obtained (see Table 4) produced a primary irritant score of 3.2 and would be considered a probable primary skin irritant based upon the assumption that erythema present at the site of application was masked by necrosis.

This material was also considered as a corrosive substance as evidenced by tissue destruction at the site of application.

Tributyltin Chloride: Primary Skin Irritation in Rabbits.
(Standard Technique)

TABLE 4. Evaluation of Primary Skin Reaction in Albino Rabbits.

| Animal Number | Sex | Initial Body Wt. | Erythema (Hours) 24 | 48 | 72 | Edema (Hours) 24 | 48 | 72 |
|---|---|---|---|---|---|---|---|---|
| Intact: | | | | | | | | |
| 8325 | M | 1875 | 1.0 | 2.0 | 2.0 | 2.0 | 2.0 | 2.0 |
| 8326 | M | 2010 | 0.0 | 0.0 | 0.0 | 2.5 | 3.0 | 3.0 |
| 8343 | F | 1888 | 1.0 | 1.5 | 2.0 | 2.0 | 3.0 | 3.0 |
| Total Values[1] | | | 0.7 | 1.2 | 1.3 | 2.2 | 2.7 | 2.7 |
| Abraded: | | | | | | | | |
| 8324 | M | 1950 | 1.0 | 1.0 | 2.0 | 2.0 | 3.0 | 2.5 |
| 8340 | F | 2390 | 1.0 | 1.0 | 2.0 | 2.0 | 3.0 | 2.5 |
| 8342 | F | 1945 | 0.5 | 0.0 | 0.5 | 2.5 | 2.0 | 2.5 |
| Total Values[1] | | | 0.8 | 0.3 | 0.8 | 1.8 | 2.2 | 2.3 |

Total Values[1] for erythema and eschar formation (24 hrs and 72 hrs, intact and abraded animals): 3.6

Total Values[1] for edema formation (24 hrs and 72 hrs, intact and abraded animals): 9.0

Sum of 8 Values divided by 4 equal primary irritant score = $\frac{12.6}{4}$ = 3.2*

* A primary irritant must total a score of 5 or more.

Value[1] - The Value[1] recorded for each reading is the average value of all animals in this group.

VIII. PRIMARY SKIN IRRITATION IN ALBINO RABBITS (M & T Technique)

A. METHOD:

A total of six albino rabbits, equally divided as to sex and ranging in weight from 1820 to 2430 grams were used. The animals were prepared for treatment by close clipping of the hair of the dorsal skin of each rabbit with an electric clipper. In addition, the clipped skin of one-half of the rabbits was abraded by producing shallow incisions with a scalpel blade over an area approximately three inches square.

The test compound was applied once only in a total amount of 0.5 ml. to the prepared back of each rabbit. Following application of the test material the area of application was covered with gauze and each animal wrapped with an elastic bandage.

The animals were than immobilized in stocks for a period of five minutes to permit percutaneous absorption and to prevent oral ingestion of the test material. At the end of the five minute period of confinement in the stocks, the bandages were removed and the back of each animal was gently washed with Zest soap and rinsed with tepid tap water. This wash and rinse procedure was repeated two additional times for a total of three washes and rinses. The site of application was then examined for evidence of irritation.

All skin reactions were scored according to the code on the following page.

| Erythema and Eschar Formation: | Value* |
|---|---|
| No erythema | 0 |
| Very slight erythema (barely perceptible) | 1 |
| Well defined erythema | 2 |
| Moderate to severe erythema | 3 |
| Severe erythema (beet redness) to slight eschar formation (injuries in depth) | 4 |

| Edema Formation: | |
|---|---|
| No edema | 0 |
| Very slight edema (barely perceptible) | 1 |
| Slight edema (edges of area well defined by definite raising) | 2 |
| Moderate edema (raised approximately 1.0 mm.) | 3 |
| Severe edema (raised more than 1.0 mm. extending beyond the area of exposure) | 4 |

* The "Value" recorded for each reading is the average value of 6 or more animals subjected to the test.

The values for erythema and eschar formation at 24 hours and at 72 hours for the intact animals' skin were added to similar values obtained for the abraded skin animals. (A total of 4 values).

Similarly, the values for edema formation at 24 and 72 hours for intact and abraded skin animals were added together (a total of 4 values). The primary irritant score is the sum of the 8 values divided by 4. As scored by this method, a primary irritant is a substance which is not corrosive, but which results in a score of 5 or more. (Section 191.1 (g)(2)) of the regulations of the Federal Hazardous Substances Labeling Act).

B. RESULTS:

Following the wash five minutes after application of the test material, slight erythema was observed in all animals tested. No edema was evidenced at this time.

At 24 hours, slight to moderate erythema was observed in five of six rabbits and slight to moderate edema in all of the animals tested. Results of observations conducted at 48 and 72 hours were essentially similiar to those observed at 24 hours. That animal which did not exhibit erythema showed marked necrosis at the site of application.

It is of interest to note that the abraded animals exhibited a lesser degree of irritation then those rabbits in the intact skin group.

All of the animals tested exhibited necrosis and five of six showed atonia at the application site. One animal at 72 hours exhibited prostration, cyanosis and hypothermia.

This substance when applied in the manner described would be considered a corrosive substance and a probable primary skin irritant.

Tributyltin Chloride: Primary Skin Irritations in Rabbits. (M & T Technique)

TABLE 5. Evaluation of Primary Skin Reactions in Albino Rabbits.

| Animal Number | Sex | Initial Body Wt. | Erythema Min. 5 | Erythema Hours 24 | Erythema Hours 48 | Erythema Hours 72 | Edema Min. 5 | Edema 24 | Edema H |
|---|---|---|---|---|---|---|---|---|---|
| Intact: | | | | | | | | | |
| 8327 | M | 2430 | 1.0 | 2.5 | 2.5 | 2.5 | 0 | 3.0 | 3 |
| 8328 | M | 2200 | 1.0 | 1.0 | 2.5 | 2.5 | 0 | 3.0 | 3. |
| 8346 | F | 1890 | 0.5 | 2.0 | 2.0 | 2.0 | 0 | 3.0 | 3 |
| Total Value[1] | | | 0.8 | 1.8 | 2.3 | 2.3 | | 3.0 | 3. |
| Abraded: | | | | | | | | | |
| 8322 | M | 1820 | 1.0 | 0 | 1.5 | 0 | 0 | 1.5 | 2. |
| 8341 | F | 2425 | 1.0 | 0 | 0 | 0 | 0 | 3.0 | 3. |
| 8344 | F | 2410 | 1.0 | 2.0 | 2.0 | 2.0 | 0 | 3.0 | 3. |
| Total Value[1] | | | 1.0 | 0.7 | 1.2 | 0.7 | | 2.5 | 2. |

Total Values[1] for erythema and eschar formation (24 hrs and 72 hrs., ir and abraded animals): 5.5

Total Values[1] for edema formation (24 hrs., and 72 hrs., intact and abr animals): 11.2

Sum of 8 values divided by 4 equal primary irritant score = $\frac{16.7}{4}$ = 4.2

** A primary irritant must total a score of 5 or more.

Value[1] - The value[1] recorded for each reading is the average value of a animals in this group.

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